REMARKS

Entry of this Amendment is proper under 37 C.F.R. § 1.116 because the Amendment places the application in condition for allowance for the reasons discussed herein; and does not raise any new issues requiring further search and/or consideration. Entry of the Amendment is thus respectfully requested.

As noted in the Office Action Summary, claims 1-18, 20-24 and 27-28 are currently pending. Claims 1, 21-24 and 27-28 have been amended herein to recite that the cleavage of the fragment in the mass spectrometer to release the mass label is achieved via collision. Basis for this amendment may be found in the specification and claims as-filed, especially at page 35, which discusses collision induced cleavage in detail. Thus, no new matter is introduced by way of the present Amendment.

Rejections under 35 U.S.C. § 103

Claim 1 stands rejected under 35 U.S.C. § 103(a) as purportedly obvious over Southern *et al.* (WO 95/04160) in view of Smith (*Nature*, 349: 812-813 (1991). The Office Action states that length-based separation using capillary electrophoresis was well known in the art at the time the instant invention was made as taught by Smith who discloses capillary electrophoresis provides for rapid and sensitive analysis of long DNA sequences.

Claims 2-18 and 20-26 stand rejected under 35 U.S.C. § 103(a) as purportedly unpatentable over Southern *et al.* in view of Ness *et al.* (U.S. Patent No. 6,027,890), Alberts (*Molecular Biology of the Cell*, 198 (1994)) and Smith. The Office Action states that it would have been obvious to the skilled artisan at the time the claimed invention was made to modify the population of DNA fragments of Southern *et al.* and to provide fragments having all possible lengths as taught by Ness *et al.* for the obvious benefit of characterizing DNA of interest completely by characterizing complementary fragments of all possible lengths.

Claim 28 stands rejected under 35 U.S.C. 103(a) as purportedly being unpatentable over Southern *et al.* The Office Action states that it would have been obvious to one of

ordinary skill in the art at the time the claimed invention was made to modify the population of DNA fragments of Southern *et al* and to provide fragments having all possible lengths as disclosed by Ness *et al.* for the obvious benefit of characterizing DNA of interest completely by characterizing complementary of all possible lengths. Applicants respectfully traverse.

Before turning to the cited references, Applicants note that independent claims 1, 21-24 and 27-28 have been amended herein to recite that the cleavage of the fragment in the mass spectrometer to release the mass label is achieved via collision.

In order to establish a case of *prima facie* obviousness, three basic criteria must be met: (1) there must be some suggestion or motivation to modify the reference or combine reference teachings, (2) there must be a reasonable expectation of success, and (3) the prior art reference(s) must teach or suggest all of the claim limitations. *See* M.P.E.P. §2142. Applicants respectfully submit that these criteria have not been met in the present Office Action.

Turning first to the primary reference, Southern *et al.*, Applicants submit that this reference fails to disclose or even suggest the cleavage of each fragment in the mass spectrometer by collision to release its mass label, as recited by claim 1 of the present application.

Specifically, at pages 20 and 21, Southern *et al.* describes a method for determining nucleic acid sequences comprising separating fragments of DNA by hybridizing the fragments to immobilized oligonucleotides provided at spaced apart locations on a support, hybridizing a coded oligonucleotide reagent having a mass label to the immobilized fragment, ligating the labeled oligonucleotide to the oligonucleotide immobilized on the support, removing non-ligated reagents, recovering the mass labels, and analyzing the mass labels of each ligated reagent as an indication of the sequence for part of the fragment. The mass labels are recovered by cleaving the mass label using a laser. The mass labels are then analyzed by mass spectrometry. Accordingly, there is no disclosure of cleaving each fragment in the mass spectrometer by collision to release its mass label as recited by claim

1 of the present invention. Rather, the mass label is cleaved by photo-cleavage using a laser. As discussed on page 2 of the present specification, cleaving each fragment within the spectrometer of the present invention by collision to release its mass label possesses advantages over the use of other methods, for example, by chemical or photolytic cleavage. Through the use of mass labels which cleave within the mass spectrometer by collision, the need for expensive laser equipment, the need for an additional cleavage chamber, the need for an interface between separating the fragments and the need of determining the mass label using a mass spectrometer is avoided.

Turning to Smith, this reference discloses separation of DNA sequences on the basis of molecular weight using capillary electrophoresis in an optical system used for multiple wavelength fluorescence detection. There is no disclosure or even suggestion in Smith of using the technique of capillary electrophoresis in combination with the technique of mass spectrometry. Further, Smith fails to remedy the deficiencies of the primary reference. If Smith were combined with the primary reference, the present invention would not be achieved, as there is no suggestion of providing a mass label which is cleavable within the mass spectrometer by collision.

Furthermore, the primary reference, Southern *et al.,* discloses a method in which fragments are first separated by hybridizing to immobilized oligonucleotides at space locations on a support. The separated fragments are subsequently labeled with a mass labeled oligonucleotide reagent and the mass label is then recovered using a laser and subsequently analyzed using mass spectrometry. This method is very different from that of the present claims, which recite that the fragments are first labeled and then the labeled fragments are subsequently separated using capillary electrophoresis. In fact, in the method disclosed in Southern *et al.,* it is unclear how the fragments would be labeled as the labeling procedure is specific to fragments which have already been separated by hybridizing to immobilized oligonucleotides on a support.

The Office Action states, on page 4, first paragraph, that it would have been obvious to the skilled artisan to modify the separation of Southern *et al.* with the capillary

electrophoresis taught by Smith. Applicants submit this is not the case. Not only would it not have been obvious for the skilled artisan to combine these documents in such a way as to achieve the present invention, it is not even clear in hindsight how the skilled artisan could successfully combine these references. Claim 1 requires that a population of mass labeled DNA fragments are present. These labeled fragments are then separated using capillary electrophoresis. Thus the recitation of claim 1 completely different from Southern *et al.*, which specifies separating the fragments to be characterized first and subsequently labeling the separated fragments, *i.e.,* completely the opposite of the presently claimed method. Furthermore, even if somehow the skilled artisan were to think of mass labeling the fragments and then separating them using capillary electrophoresis, there is absolutely no suggestion of providing mass labels which are cleavable within a mass spectrometer by collision. Rather, Southern *et al.* teaches cleavage using a laser prior to analysis by mass spectrometry.

Applicants further note that the in method disclosed by Southern *et al.*, it is the target nucleic acids which are to be characterized. However, it appears that the Office Action may consider the coded oligonucleotide reagents in step c) on page 20 of Southern *et al.* to constitute the population of fragments of DNA recited in step (i) of present claim 1. Applicants note this is not the case. Step (i) of present claim 1 specifies a population of fragments of said DNA referring to the first line of claim 1, which states a method for characterizing DNA. The DNA is to be characterized in the method of Southern *et al.* as recited on page 20 is the target nucleic acid. The target nucleic acid fragments are not labeled prior to separation.

The only population of fragments of DNA which have mass labels and which are not separated prior to labeling in Southern *et al.* is the library of coded oligonucleotide reagents in step c) on page 20. However, until these coded oligonucleotide reagents are incubated with hybrids from step b) then they are not specific to the target nucleotide and contain no information of any use. Separating these fragments by capillary electrophoresis

as disclosed in Smith would not result in any useful information about the target nucleic acids.

Thus, in light of the above remarks, Applicants submit that Claim 1 is not unpatentable over Southern *et al.* in view of Smith, claims 2-18 and 20-26 are not unpatentable over Southern *et al.* in view of Ness *et al.* and Smith, and that claim 28 is not unpatentable over Southern *et al,* because there is no suggestion or motivation to modify the reference or combine reference teachings, there is not a reasonable expectation of success, and the cited references, alone or in combination fail to disclose or suggest the elements of the present claims. Applicants request that this rejection be withdrawn.

CONCLUSION

Based on the foregoing, this application is believed to be in condition for allowance. A Notice to that effect is respectfully solicited. However, if any issues remain outstanding after consideration of this Amendment and Reply, the Examiner is respectfully requested to contact the undersigned so that prosecution may be expedited.

In the event any further fees are due to maintain pendency of this application, the Examiner is authorized to charge such fees to Deposit Account No. 02-4800.

Respectfully submitted,

BURNS, DOANE, SWECKER & MATHIS, L.L.P.

Date: November 10, 2003 By: _____

Deborah H. Yellin
Registration No. 45,904

P.O. Box 1404
Alexandria, Virginia 22313-1404
(703) 836-6620